CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-395	TRADE NAME:	Spiriva Handihaler
APPLICANT/SPONSOR:	Boehringer Ingelheim	USAN NAME:	tiotropium bromide inhalation powder
DEPUTY DIRECTOR:	Eugene Sullivan, MD FCCP		
DIVISION DIRECTOR:	Badrul Chowdhury, MD PhD	CATEGORY:	Anticholinergic bronchodilator
DUE DATE:	January 30, 2004	ROUTE:	Oral Inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
December 30, 2003	n/a		Electronic Document Response to 12/23/03 FDA labeling comments and IR

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a Medical Officer Review of a submission dated 12/30/03. This NDA is currently undergoing second-cycle review, following an AE action taken during the first cycle. On 12/23/03, the Division communicated a number of labeling comments to the Applicant. On the same date, the Division issued a clinical Information Request (IR). This submission provides the Applicant's response to both of those communications. This document will summarize and review the Applicant's responses, and will establish a clinical path forward.

OUTSTANDING ISSUES:

The Division will convey its responses to the issues raised in this submission, either by fax or in a telephone conference. (See sections entitled Comments to Applicant, and Phase 4 Commitments in the text of this review.)

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	____ SAFE TO PROCEED	____ CLINICAL HOLD		
NDA/SUPPLEMENTS:	____ FILEABLE	____ NOT FILEABLE		
	____ APPROVAL	____ APPROVABLE	____ NOT APPROVABLE	
OTHER ACTION:				

I. Applicant's Response to DPADP's 12/23/03 Clinical Labeling Comments

On December 23, 2003, DPADP communicated clinical labeling comments to the Applicant. The clinical comments are identified as numbers 1-17 in the 12/23/03 fax to the Applicant. The genesis of these comments can be found in the Medical Officer Review of the Applicant's 7/31/03 Complete Response submission. In the current submission (12/30/03), the Applicant states that it has incorporated all but two of the revisions proposed by the Division. The two clinical revisions that the Applicant has not agreed to are numbers 3 and 15.

A. Comment 3

Comment 3 read: *"The following statements should be added to the CLINICAL PHARMACOLOGY section of the package insert:* [redacted]

[redacted]

[redacted]'" The Applicant requests that this comment be reconsidered and that the Division consult with the DCRDP on this matter. The Applicant refers to its 12/11/03 submission on this issue, and points out that a QT effect is not expected for an anticholinergic drug and was not seen in other trials. **Reviewer's Comment: As discussed in the Medical Officer Review of the 7/31/03 and 12/11/03 submissions, the finding of increased frequency of QTc outliers in the tiotropium treatment group in study 205.131 is potentially clinically significant, and cannot be ignored. Because of the deficiencies in the collection of ECG data, the prior clinical studies cannot be used to definitively discount the findings in Study 205.131. It is true that, as a class, anticholinergic drugs are not known to prolong the QT, but that does not exclude the possibility that this specific drug may have such an effect. In order to address the Applicant's concern the proposed language should be modified to include the fact that prolongation of the QT interval was not observed in other studies: *"In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline corrected QT interval of 30-60msec was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. Other clinical studies of tiotropium have not detected an effect of the drug on the QT interval."***

The Applicant should commit to further study of this issue during Phase 4, as discussed in the Medical Officer Review of the 7/31/03 and 12/11/03 submissions.

B. Comment 15

Comment 15 read: *"Modify the Adverse Event table to provide the incidences of specific adverse events in terms of the numbers of patients, in addition to the percentages."* The

Applicant has drafted a table that includes both the numbers of patients (n) and the percentages (%) [page 10]. However, the Applicant states that the inclusion of both the numbers and percentages makes the table more difficult to interpret because the numbers of patients enrolled across treatment groups are different. The Applicant believes that the prior version of the table, which included the only the percentages in the body, with the numbers of patients in each treatment group included in the header, adequately conveyed the information and is preferable. **Reviewer's Comment: The Applicant's proposal not to modify the prior version of this table is acceptable.**

II. Applicant's Response to DPADP's 2/23/03 Information Request

On December 23, 2003, DPADP communicated a clinical Information Request (IR) to the Applicant. The IR read: *"The application states that the Dutch authorities have requested that the Summary of Product Characteristics document be revised to expand the statements regarding allergic reactions. You have proposed to add reference to post-marketing events of urticaria and pruritis in the US product label. Provide further details and explanation regarding the data that generated these concerns."*

The Applicant states that the request was based upon spontaneous AE reports received by the Applicant, and reported in Periodic Safety Update Reports (PSUR). The submission implies that the specific events that prompted the Dutch authorities' request occurred during the reporting period for the third PSUR (October 10, 2002, to April 9, 2003). During this period, the Applicant estimates that [redacted] capsules were sold, and that this corresponds to approximately [redacted] patient years of exposure. During this period, four AE reports were coded as "urticaria NOS," all of which were non-serious. The submission includes a brief summary of each of these cases. In addition, the submission states that a search of its database using the preferred term "urticaria NOS" revealed two additional cases, which were "outside the scope" of the PSUR [page 13]. In one of these cases, positive de- and re-challenges were observed. Also during the period corresponding to the third PSUR, pruritis as a separately coded AE appeared in 26 cases (preferred term "pruritis NOS" and "pruritis generalized"). In 15 cases pruritis was mentioned with no other relevant adverse events referring to allergic reactions or skin reactions. The Applicant states that, given the fact that allergic reactions may occur as a result of exposure to tiotropium, it was judged that there was sufficient evidence to merit inclusion of specific descriptions of possible allergic events (urticaria and pruritis) in the Summary of Product Characteristics.

The submission also references specific AEs reported during the period corresponding to the fourth PSUR (April 1, 2003, to September 30, 2003). During this period the Applicant estimates that [redacted] capsules were sold, and that this corresponds to approximately [redacted] patient years. Based on spontaneous AE reports during this period, the Applicant has proposed to foreign regulatory authorities that "epistaxis" and "palpitations" be added to the safety section of the Summary of Product Characteristics. During this period there were six cases of epistaxis, one of which was reported as serious. Given the possibility that mucosal drying, which may be a pharmacologic effect of this anticholinergic drug, could lead to epistaxis, the Applicant believes it would be appropriate to include "epistaxis" in the product label. During the reporting period corresponding the fourth PSUR, there were 18 cases of "palpitations," of which four were reported as serious. The Applicant points out that the currently proposed product label includes reference to supraventricular events.

Reviewer's Comment: The currently proposed version of the product label includes "atrial fibrillation" and "supraventricular tachycardia," which are both described as "adverse events in the clinical trials with an incidence of <1%." Based on these reports, the Applicant proposes to add "epistaxis" and "palpitations" to the list of adverse events reported in the worldwide post-marketing experience. **Reviewer's Comment: This proposal is acceptable.**

III. Comments to Applicant

The following comments will be conveyed to the Applicant, either by fax or in a telephone conference.

1. **In regard to your objection to Comment number 3 in the Division's 12/23/03 fax, the Division maintains that the finding of increased frequency of QTc outliers in the tiotropium treatment group in study 205.131 is potentially clinically significant, and cannot be ignored. Because of the deficiencies in the collection of ECG data, the prior clinical studies cannot be used to definitively discount the findings in Study 205.131. While it is true that, as a class, anticholinergic drugs are not known to prolong the QT, that does not exclude the possibility that this specific drug may have such an effect. In order to address your stated concern, the proposed labeling language has been modified. The following statement should be added to the CLINICAL PHARMACOLOGY section of the package insert:** ***"In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline corrected QT interval of 30-60msec was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. Other clinical studies of tiotropium have not detected an effect of the drug on the QT interval."***
2. **In regard to your objection to Comment number 15 in the Division's 12/23/03 fax, your proposal not to modify the prior version of this table is acceptable.**
3. **Your proposal to add "epistaxis" and "palpitations" to the list of adverse events reported in the worldwide post-marketing experience is acceptable.**

IV. Phase IV Commitment

As discussed in the Medical Officer Review of the 7/31/03 and 12/11/03 submissions, ECG data from a randomized, placebo-controlled trial raised the possibility that tiotropium might have a clinically meaningful effect on the QT interval. Although other clinical trials did not raise this potential safety signal, it must be noted that the pivotal trials were not designed and conducted in such a way as to carefully evaluate possible ECG effects. For instance, the protocols for the pivotal trials did not specify the timing of the ECGs in relation to dosing. *The Applicant should commit to conduct a clinical study to thoroughly investigate the effects of tiotropium on the QT interval. Such a study could be performed in normal volunteers or COPD patients, should investigate effects following a single dose and at steady state, and*

should include the proposed marketed dose, as well as a higher dose. The Applicant should submit the proposed study protocol to the Division for comments, prior to initiating the study.

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/s/

Eugene Sullivan
1/7/04 11:48:37 AM
MEDICAL OFFICER

Badrul Chowdhury
1/7/04 12:55:24 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-395	TRADE NAME:	Spiriva Inhalation Powder
APPLICANT/SPONSOR:	Boehringer Ingelheim Pharmaceuticals	USAN NAME:	tiotropium bromide
MEDICAL TEAM LEADER (ACTG):	Eugene J. Sullivan, MD FCCP		
DIVISION DIRECTOR:	Badrul Chowdhury MD, PhD	CATEGORY:	Anticholinergic bronchodilator
DUE DATE:		ROUTE:	Oral inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
July 31, 2003	August 4, 2003	Complete Response to 12/20/02 action letter	Electronic submission
June 11, 2003	June 12, 2003	I46,687 N182 IM	ECG data report submitted to IND
December 11, 2003	December 12, 2003	N-000-BM	Response to information request

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a Medical Officer Review of Boehringer Ingelheim's complete response to an FDA Approvable action. On December 12, 2001, BI submitted an original NDA (21-395) for tiotropium bromide inhalation powder. On December 20, 2002, the Agency issued an Approvable action for the application. The clinical review team had determined that the data were adequate to support approval; however, an Approvable action was taken because of numerous outstanding CMC issues. The current submission represents the Applicant's response to the comments in the December 20, 2002 letter. From a clinical perspective, the current submission contains two important elements. The first is the safety update. The second is the Applicant's proposed labeling. This document will review each of these elements.

From the clinical perspective, this application remains sufficient for approval, pending labeling negotiations.

OUTSTANDING ISSUES:

The labeling comments in this Review will be sent to the Applicant.

RECOMMENDED REGULATORY ACTION (CLINICAL RECOMMENDATION)

IND/NEW STUDIES:	____	SAFE TO PROCEED	____	CLINICAL HOLD	
NDA/SUPPLEMENTS:	____	FILEABLE	____	NOT FILEABLE	
	X	APPROVAL	____	APPROVABLE	____ NOT APPROVABLE
OTHER ACTION:					

I. Background

This is a Medical Officer Review of Boehringer Ingelheim's complete response to an FDA Approvable action. On December 12, 2001, BI submitted an original NDA (21-395) for tiotropium bromide inhalation powder. The application was discussed at a meeting of the Pulmonary-Allergy Drug Products Advisory Committee on September 6, 2002. On December 20, 2002, the Agency issued an Approvable action for the application. The clinical review team had determined that the data were adequate to support approval; however, an Approvable action was taken because of numerous outstanding CMC issues. During that review cycle initial labeling negotiations were undertaken. The current submission represents the Applicant's response to the comments in the December 20, 2002 action letter. From a clinical perspective, the current submission contains two important elements. The first is the safety update. The second is the Applicant's proposed labeling. This document will review each of these elements.

II. Safety Update

The Safety Update included in the current submission uses a cut-off date of December 13, 2002. It includes:

- — adverse event data from four completed clinical trials (205.215, 205.218, 205.131, and 205.220),
- — blinded safety data from twelve ongoing trials,
- — preliminary unblinded data from three "clinically complete" trials (trials that are recently completed and for which final study reports have not yet been prepared),
- — an update on post-marketing data from countries where the drug is currently approved,
- — approved product labeling from Canada, Australia, and New Zealand, and
- — analyses of ECGs that were performed in clinical trials submitted with the original NDA submission.

The adverse event data are provided in a non-integrated fashion.

A. Completed Clinical Trials

The safety update includes reports from three completed clinical trials in which patients with COPD received tiotropium. In these studies, safety was monitored through adverse event reporting, vital signs, physical examination, and ECGs [U03-3210.pdf/p19]. **Reviewer's Comment: The safety update does not provide the data regarding vital signs or physical examination.** The Applicant states that the analysis of adverse events from these three clinical trials does not provide new insights into the safety profile of tiotropium [U03-3210.pdf/p12]

1. 205.215/U02-1622: This was a randomized, double-blind, placebo-controlled, parallel group trial performed at ten study centers. The trial was designed to correlate the effects of 12-weeks of once-daily treatment with tiotropium on lung

function and dyspnea in patients with COPD. During the 12-week treatment period, clinic visits were scheduled every 6 weeks. A total of 100 patients were randomized, 46 to tiotropium and 54 to placebo. The large majority of subjects were male (94%) [U03-3210.pdf/p82]. All subjects with non-missing data on race were White. The occurrence of overall adverse events, serious adverse events, and adverse events leading to discontinuation did not suggest a safety concern regarding tiotropium. One event of potential significance occurred in a patient in the tiotropium group, who discontinued the study due to a serious adverse event of peripheral neuropathy [U03-3210.pdf/p38, 91, 94, 96].

2. 205.218/U02-3256: This was a randomized, double-blind, placebo-controlled, parallel group trial performed at six study centers [U03-3210.pdf/p34]. The trial was designed to investigate the effects of 28 days of treatment with tiotropium on inspiratory capacity in patients with COPD. During the 28-day treatment period, clinic visits were scheduled every 2 weeks. A total of 81 patients were randomized, 40 to tiotropium and 41 to placebo. Seventy-eight of the patients were White. Adverse events were reported in 35% and 24% of patients in the tiotropium and placebo groups, respectively. There were two deaths in the trial, one each in the tiotropium (COPD exacerbation) and placebo (multi-organ system failure following coronary artery bypass surgery) groups [U03-3210.pdf/p39-40]. The pattern of adverse events, serious adverse events, and events leading to discontinuation did not suggest a previously unidentified safety issue for tiotropium.

3. 205.131/U02-1202: This was a multi-center, randomized, double-blind trial to investigate whether tiotropium can increase exercise tolerance as measured by endurance time during constant work rate cycle ergometry at 75% of maximal work capacity in COPD patients with static lung hyperinflation during six weeks of treatment [U03-3210.pdf/p35]. A total of 198 patients were randomized, 98 to tiotropium and 100 to placebo. All patients except one were White. The pattern of adverse events, serious adverse events, and events leading to discontinuation did not suggest a previously unidentified safety issue for tiotropium.

In summary, the pattern of adverse events, serious adverse events, and events leading to discontinuation in the three completed clinical trials did not suggest a previously unidentified safety issue for tiotropium.

B. Ongoing Clinical Trials

1. Blinded Safety Data

The safety update contains blinded safety data from twelve ongoing trials [U03-3210/p53-56]. Due to the blinded nature of the data, no conclusions may be drawn.

2. Unblinded Safety Data

The safety update contains preliminary unblinded data from three "clinically complete" trials (trials that are recently completed and for which final study reports have not yet been prepared) [U03-3210/p56-59]:

— 205.226: a four-week safety and efficacy study comparing once daily tiotropium 18mcg and 36mcg with oxitropium bromide MDI 200mcg TID in 201 COPD patients in Japan

— 205.227: an open-label one-year safety and efficacy study comparing once daily tiotropium 18mcg with oxitropium bromide MDI 200mcg TID in 161 COPD patients in Japan

— 205.243: a safety and efficacy study comparing once daily tiotropium inhalation capsules 18mcg with Atrovent (ipratropium bromide) MDI 40mcg QID in 215 COPD patients in the Philippines

In Trial 205.226, GI disorders were more frequent in the tiotropium 36mcg group (31.8%) than in the other two groups (6.0% and 5.9%) [U03-3210/p192-4]. This difference was primarily due to an increased frequency of dry mouth (27.3% vs. 1.5% and 3% in the other groups) and constipation (6.1% vs. 0% in the other groups) in the tiotropium 36mcg group. In Trial 205.227, dry mouth was more frequent in the tiotropium (18mcg) group (17.3% vs. 5.9%), but COPD exacerbations (10.9% vs. 17.6%) and pneumonia (2.7% vs. 9.8%) were less frequent in the tiotropium group. In Trials 205.227 and 205.243, tiotropium was also associated with a greater frequency of hyperuricemia than the comparator (3.6% vs. 0%, and 2.9% vs. 0%). The data from these three "clinically complete" active-controlled studies do not suggest previously unknown adverse effects of tiotropium.

C. Foreign Post-marketing Data

Tiotropium bromide has been approved for marketing in 40 countries, and, as of December 13, 2002, the product has been launched in 12 countries [U03-3210.pdf/p60]. In the EU, the Mutual Recognition Procedure was used, with Netherlands serving as the Reference Member State. In addition to EU states, other notable countries in which the product has been approved include Australia, Canada, New Zealand, South Africa, and Switzerland. The first launch occurred in June, 2002.

The Applicant states that post-marketing experience has not led to any reports of new adverse effects, warning letters to physicians, or "major changes in marketing status or labeling information" [U03-3210.pdf/p63]. However, the Dutch Authorities, who served as the Reference Member State in the Mutual Recognition Procedure, made a request to "expand the statements regarding allergic reactions: swelling of tissue and extremities, pruritis, and leg edema/angio-edema." Based on this request, the Applicant is proposing to add a post-marketing section to the Adverse Reactions section of the US product label, in which to include the adverse events urticaria and pruritis [U03-3210.pdf/p63]. **Reviewer's Comment: The specific reasons for the Dutch request are not clear in the Application. In the section describing post-marketing reports of adverse events, the Applicant includes the following language: "Cases of urticaria and pruritis (none serious) were reported and might be considered as adverse events in the context of allergic reactions. While allergic reactions including angioedema are included as adverse reactions that may be observed with tiotropium, urticaria and pruritis have not been specifically noted." [U03-3210.pdf/p67] The meaning of these statements is not clear.**

The Applicant states that there have been no refusals of drug approval based on safety grounds from any foreign regulatory body. The Applicant states that —

Reviewer's Comment: The Application does not describe the nature of this

The Application presents post-marketing data for the period of June 1, 2002, to December 14, 2002. Over this period, a total of 354 reports of adverse drug reactions were received [U03-3210.pdf/p65]. Of these, 66 (18.6%) were reported as serious, and 14 (4.0%) were fatal. The causes of death were consistent with the elderly COPD population. There were two cases of sudden death, occurring three and nine days after initiation of tiotropium.

D. Electrocardiographic Data

Electrocardiograms from the one-year placebo-controlled trials (205.117/U99-3169, 205.128/U00-3170), six-month salmeterol- and placebo-controlled trials (205.130/U00-1236, 205.137/U001231), and exercise trial (205.131/U02-1202) were sent to a central laboratory (or a "high-resolution" measurement of cardiac intervals. Using digitization software, cardiac intervals were measured (RR, PR, QRS, and QT) and corrected QT intervals (QTc) were calculated using both Bazett's (QTcB) and Fredericia's (QTcF) formulas [U03-3210.pdf/p45]. Analyses of change from baseline to average on treatment value, change from baseline to maximum on treatment value were performed. In addition, for QT and QTc intervals, analyses of the numbers of patients with on-treatment values >500 msec (when not present at baseline) were performed. Also, for QTc, analyses of numbers of patients demonstrating a categorical change from baseline (<30msec, 30-60msec, and >60msec) were performed. Outlier analyses were performed for PR (change from baseline ≥25%, when PR >200msec), QRS (change from baseline ≥25% when QRS >100msec), and heart rate (25% decrease to <50bpm, and 25% increase to >100bpm).

In the one-year, placebo-controlled trials, ECGs were performed at baseline and every 3 months. **Reviewer's Comment: The submission does not state the timing of these ECGs in relation to dosing (e.g. trough, Cmax, etc.). This question was raised during the review of the original NDA submission. In response to a request for information from the Division, the Applicant stated that the protocols did not specify the timing of the ECGs in relation to the administration of study drug, and that information was not captured in the case report forms. This is a significant limitation of the data.** In these two trials there were 2,359 ECGs completed by 518 tiotropium patients, and 1,505 ECGs completed by 343 placebo patients [U03-3210.pdf/p46-47]. According to the summary table provided in the safety update, there was very little difference between active and placebo in terms of the interval analyses described above. The percentage of patients with "tachycardia events," defined as a ≥25% increase in heart rate to >100 bpm, was 2.3% in the tiotropium group, and 1.7% in the placebo group. The mean change in QT was 0msec in both groups, and the mean change in both QTcB and QTcF was 1msec in the tiotropium group and 0msec in the placebo group. The incidence of QTcB and QTcF outliers, based on categorizations described above, was similar between groups, with the possible exception of the percentages of patients exhibiting a >60msed change in QTcB (2.7% and 1.5% in the tiotropium and placebo groups, respectively) and QTcF (1.4% and 0.3% in the tiotropium and placebo groups, respectively).

In the six-month salmeterol- and placebo-controlled trials, ECGs were performed at baseline and end of treatment. **Reviewer's Comment: No further information regarding the timing of the ECGs is provided.** In these two trials there were a total of 390 ECGs performed in tiotropium patients, and 364 ECGs performed in placebo patients [U03-3210.pdf/p48]. **Reviewer's Comment: These numbers seem odd given that there were 346 tiotropium patients and 315 placebo patients, each of whom were to have undergone two ECGs.** According to the summary table provided in the safety update, there was very little difference between active and placebo in terms of the interval analyses described above [U03-3210.pdf/p49]. The mean change in QT was -4.5 msec in the tiotropium group and –4.0 msec in the placebo group. The mean change in QTcB was 2msec in the tiotropium group and 0msec in the placebo group, and the mean change in QTcF was -0.3msec in the tiotropium group and -1.2msec in the placebo group. The incidence of QTcB and QTcF outliers, based on categorizations described above, was similar between.

In the exercise trial (Study 205.131), resting supine ECGs were obtained on Days -15, 0, 21, and 42 (pre-dose), and 14 days after the treatment period. During exercise testing, ECGs were recorded before loadless pedaling, at peak/end of exercise, and in the case of pathologic findings during exercise testing [U03-3210.pdf/p12]. Exercise tests were performed in the sitting position on Days -10, -5, 0, 21, and 42. The summary of the ECG data provided in the safety update is somewhat difficult to interpret because apparently the resting and exercise ECGs have been considered together (although, surprisingly, the mean heart rate actually decreased from baseline) [U03-3210.pdf/p51]. The summary data generally do not suggest a notable drug effect on the ECG intervals. However, one interesting finding is that, although the mean QTcB and QTcF were essentially unchanged in both groups, *the number of subjects with changes from baseline QTcB and QTcF of 30-60msec was notably higher in the tiotropium group.* In the tiotropium group 20 (20.4%) and 16 (16.3%) patients had changes of this magnitude in QTcB and QTcF, respectively, compared with 12 (12%) and 1 (1%) in the placebo group. There was one subject who exhibited an increase in QTcB >60msec. This subject was in the tiotropium group. No subjects exhibited an increase in QTcF >60msec.

The finding of increased QTc outliers described above was further explored. In a submission to the IND (46,687) dated June 11, 2003, the Applicant provided the Cardiovascular ECG Data Reports, which formed the basis of the summaries included in the current submission. The Cardiovascular ECG Data Report for the exercise study (Study 205.131) is included in the June 11, 2003 submission (Document Number U03-1390, Vol. 6 of 15). In this report, resting ECGs (supine and sitting, combined) are separated from exercise ECGs. The QTcB and QTcF outlier data described above are stated to represent resting ECGs [Vol. 6, p10]. The study report states that the differences between treatment groups in the numbers of subjects demonstrating an increase of 30-60msec in QTcB (20% vs. 12%) and QTcF (16% vs. 1%) are "regarded as nonspecific" [Vol. 6, p14]. This Reviewer could not locate QTc data performed on exercise ECGs.

In a fax dated November 30, 2003, the Division requested that the Applicant comment on the potential clinical significance of the finding of increased QTc outliers in Study 205.131, and to provide a proposal to further investigate possible QTc effects of tiotropium. The Applicant responded in a submission dated December 11, 2003. In this response, the Applicant concludes that tiotropium does not increase QT intervals, and proposes no further

study of the issue. It should be noted that the Applicant is currently enrolling patients in a 12-week trial of 150 patients, in which Holter monitoring will be obtained at baseline, and after 8 and 12 weeks of treatment. ECGs will be obtained at baseline, and pre- and 5 minutes post-dosing after 8 and 12 weeks of treatment. The submission includes a response from the Applicant, as well as letters from two consulting cardiologists addressing the issue. The Applicant makes the following arguments in support of its claim that tiotropium does not increase QT intervals:

— Anticholinergic drugs have not previously been shown to increase QT intervals. **Reviewer's comment: We agree that anticholinergics have not been associated with QT prolongation. This is in part why the cardiac safety database was considered to be adequate for approval during the review cycle and why, prior to the receipt of the data from Study 205.131, the Division had not suggested that a thorough evaluation of QT effect would be necessary.**

— An increase in QTc of 30-60msec is a "nonspecific finding."

— There was no evidence of a more significant effect on QT, such as outliers with increases >60msec, or QTc > 500msec. **Reviewer's Comment: It is true that there was not clear signal in these categories. It should be noted that, in fact, one patient exhibited a change from baseline of >60msec in QTcB. This patient received tiotropium.**

— Drugs that have no signal of an effect on mean QT/QTc are not associated with a signal on outlier analyses. **Reviewer's Comment: It is not clear that this assertion is correct. This is why categorical ("outlier") analyses are customarily requested, in addition to analyses of central tendency (e.g. mean values). Drug effects, both therapeutic and adverse, may in part be genetically determined. It seems odd to discount the possibility that there might be a population of patients who exhibit a drug-related QT prolongation, simply because the population is not large enough to affect the mean values in a clinical trial. Such a population could exist based on genetically determined differences in absorption/metabolism of a drug, receptor characteristics, or other unrecognized relevant differences. Finally, until a thorough evaluation for QT effect has been undertaken, it would not be appropriate to determine that tiotropium has no effect on mean QT/QTc.**

— No QT/QTc signal was detected in prior clinical trials. **Reviewer's Comment: It should be noted that the ECG data from the previous studies was limited. As noted elsewhere in this Review, the timing of the ECGs in relation to dosing was not specified in the protocols. One of the Applicant's consulting cardiologists, Dr. [redacted] noted in his letter that the prior trials were "rather lacking in ECG robustness in terms of frequency of ECG sampling and adequate baseline determinations."**

— The low occurrence of outliers in the placebo group in Study 205.131 (1%) is likely spurious because, in two large placebo-controlled studies, the incidence of outliers (30-60msec) was 5-15%. **Reviewer's Comment: The low occurrence of outliers**

in the placebo group may be spurious. However, it is not clear that data from the prior trials can be used to establish this definitively, given their limitations.

— Additional analyses of data from Study 205.131 suggest that patients who were outliers did not consistently demonstrate outlier values on ECGs.

— Baseline values were determined using mean values from "up to" five pre-dose ECGs. Post-hoc determination of baseline values using the median, rather than the mean value, showed less of a signal. **Reviewer's Comment: Because of its post-hoc nature, this analysis is not very convincing.**

Reviewer's Comment: The finding of increased frequency of QTc outliers in the tiotropium treatment group is potentially clinically significant, and cannot be ignored. Because of the deficiencies in the collection of ECG data, the prior clinical studies cannot be used to definitively discount the findings in Study 205.131. However, the data available to date cannot be considered to establish a drug effect on QT, and the issue should not preclude approval of this drug. Nonetheless, this finding should be included in the product label, and the Applicant should commit to further investigation of this finding in a thorough Phase 4 study.

E. Other Data

The safety update also included reference to three additional sources of relevant information:

— B1236/U03-1175: a 13-week preclinical study in rats examining the systemic toxicity of the principal degradation products of tiotropium bromide present at concentrations predicted to be equal to those in the drug product at the end of its shelf life. The study report for this study is included in the Pharmacology and Toxicology section of this submission. It was not reviewed for this Medical Officer Review.

— 205.239/U02-1522: a clinical pharmacokinetic/pharmacodynamic study assessing the effect of a single nebulized dose of 500mcg ipratropium bromide in 35 healthy male volunteers who had received 19 days of treatment with tiotropium inhalation capsules 18mcg daily. There was no placebo control in the tiotropium phase. The safety update contains very little data on this trial [U03-3210.pdf/p52].

— 205.220/U02-1615: a single-blind, two-center trial to assess the ease of use, administration technique, and learning retention of administration technique for the Handihaler (no active drug) in 152 subjects. Because no active drug was administered in this trial, it was not examined as part of this safety review.

III. Labeling

A. Response to Labeling Comments in the 12/20/02 Action Letter

The Division discussed various aspects of the labeling with the Applicant during the review period for the original NDA submission. The December 20, 2002 action letter included several clinical labeling comments, which referred to the November 19, 2002 version of the

draft label. These included comments regarding the proposed package insert (Action Letter Comment 19) and the Patient's Instructions for Use document (Action Letter Comment 20).

1. Package Insert

The clinical comments on the proposed package insert were: a) remove reference to the [redacted], in the figures and text describing two of the clinical trials; b) add a statement indicating that patients with narrow-angle glaucoma or symptomatic bladder outlet obstruction were excluded from the clinical trials; and c) add a sentence describing adverse ophthalmologic effects seen in a small, high-dose clinical study. In addition, the action letter also included instructions to amend the Patients Instructions for Use section of the label.

In the current submission, the Applicant has removed the references to the [redacted], in the relevant clinical trials (letter a, above). The Applicant states that once this information was removed, the order of the studies was changed in order to maintain a logical sequence. Because the [redacted] and placebo controlled studies is not discussed, the current proposal groups these among the placebo-controlled studies, rather than the active controlled studies. **Reviewer's Comment: This change is reasonable.**

In the current submission, the Applicant has also added the statement regarding exclusion of patients with narrow-angle glaucoma or bladder outlet obstruction from the clinical trials (letter b, above), and the sentence describing adverse ophthalmologic effects seen in a small, high-dose clinical study (letter c, above).

2. Patient's Instructions for Use document

The clinical comments on the Patient's Instructions for Use document were to change the wording of two sentences in the document. In the current submission, the Applicant has changed these sentences as requested.

B. Additional Labeling Changes Proposed by Applicant

The Applicant has also added new labeling language that is not directly responsive to the labeling comments in the action letter. Previously, the proposed label had simply stated that [redacted] The Applicant has now added the following language:

[Lines 172-177]

It should be noted that the primary efficacy endpoint in these trials was trough FEV_1, and not peak FEV_1. However, given the known pharmacodynamics of ipratropium, a comparison at trough (pre-dose in the morning) is not considered appropriate. For this reason the Applicant has proposed to describe the peak FEV_1 comparison. While this may be reasonable, the statement above reflects the data from only one of the two studies. In

Study 205.122B/205.126B tiotropium was *statistically* superior to ipratropium in regard to peak FEV_1 response on all treatment days except day 1. However, in Study 205.122A/205.126A, tiotropium was not statistically superior to ipratropium on this parameter on days 1, 92, or 364. Further, although statistically significant, the magnitude of the difference between tiotropium and ipratropium was small (0.08L-0.14L in Study 205.122B/205.126B and 0.00 on Day 1 and 0.04 – 0.11L during the remainder of the study in Study 205.122A/205.126A) [December 12, 2001 submission, U00-3114.pdf/p67 and U00-3113.pdf/p71]. *Because statistical superiority was not consistently demonstrated, and because the effect size of tiotropium over ipratropium was small, this newly proposed language should not be included in the label.* Finally, the last sentence adds no new information, because this information was already discussed in the one-year, placebo-controlled trials. This sentence should be deleted.

Based on the findings of the Safety Update, the Applicant has added reference to urticaria and pruritis, both of which were seen in the post-marketing experience, to the product label. The Applicant states that, apart from this addition, the Safety Update did not raise any other safety issues that should be included in the product label.

C. Additional Comments on the Proposed Labeling

The following comments on the proposed label were not previously conveyed to the Applicant. Many of these have been adopted from a consultation provided by the Division of Drug Marketing, Advertising, and Communications.

— CLINICAL PHARMACOLOGY, Mechanism of Action section: The drug is described as a [redacted] antimuscarinic (line 48). The next sentence indicates that it has similar affinity for all muscarinic receptor subtypes. Although it could be considered to be an anticholinergic that is specific for muscarinic receptors, the qualifier "[redacted]" has no particular meaning when used to qualify "antimuscarinic," and should be deleted.

— In the CLINICAL PHARMACOLOGY, Mechanism of Action section: The following two sentences should be deleted: "[redacted] (Lines 55-58) The first sentence does not clarify a mechanism of action, and would likely be used more to [redacted] which is not supported by the clinical data. The term "[redacted]" in the second sentence is not defined, apart from the observation that [redacted]

— In the CLINICAL PHARMACOLOGY, Pharmacokinetics section: the first sentence [redacted] (Line 60) is not relevant to this section, and should be deleted. This same information is included in the DESCRIPTION section.

— The proposed text describing the metabolism of tiotropium does not clearly communicate the appropriate data (lines 88-95). Dr. Fadiran, team leader in the Office of Clinical Pharmacology and Biopharmaceutics, has proposed specific text to replace the Applicant's proposed text (see Labeling Comments to be Conveyed to the Applicant, below).

— CLINICAL STUDIES section, line 141: The term " is discouraged in the current Draft Guidance on the "Clinical Studies Section of Labeling." According to the Draft Guidance, "major efficacy study" is preferred.

— CLINICAL STUDIES section, line 146: Because was not a primary endpoint, reference to should be deleted.

— CLINICAL STUDIES section: the patient population should be specified more carefully. Currently the description of the studies states only that "patients with COPD" were studied.

— In the PRECAUTIONS section, the statement that " should be modified to "Inhalation medications, including Spiriva, may cause paradoxical bronchospasm." This is the phrase used in the labels for other inhalation products (Serevent, Ventolin, Foradil). This statement should be moved to the WARNINGS section, it is more a warning of a potential adverse effect than an instruction for precautionary measures. In addition this statement is located in the WARNING section of labels for other inhalation products (Serevent Ventolin, Foradil).

— Spiriva is a long-acting anti-cholinergic medication.

The PRECAUTIONS section of the label should include such a statement.

— In the Drug Interactions section, the phrases "commonly used in COPD," and ' are redundant. The second occurrence (line 243) should be deleted.

— The Geriatric Use section includes data describing differences in adverse events based on age. This issue should be noted in the Adverse Reactions section, with reference to the Geriatric Use section. A new paragraph in the Adverse Reactions section, following line 353, should state that "In the one-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age. (See **PRECAUTIONS**, **Geriatric Use)**

— The table of adverse events includes only the percentages of patients. While this is consistent with the title of the table, a reader might misinterpret the percentages as numbers of patients. Although the product label for salmeterol products use a similar approach, the product label for a more recently approved drug, Foradil, includes both the numbers and percentages of patients in the adverse event table. The Adverse Event table should be modified to provide the numbers of patients in addition to the percentages.

— The OVERDOSAGE section should include reference to a foreign post-marketing report of a case of overdose. This case was referenced in three separate submissions

to the Agency: N-184-S2 (Letter date July 8, 2003), N-187-S2 (Letter date July 22, 2003), and N-195-S3 (Letter date September 29, 2003). This was a female patient of unknown age from Australia, who was prescribed Spiriva for the treatment of COPD. She inhaled 30 capsules over a 2.5 day period and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, Spiriva was discontinued, and the constipation was treated with an enema. Further follow-up was not provided.

— The Dosage and Administration section states that no dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, the Precautions section states that Spiriva use should be monitored closely in patients with moderate to severe renal impairment. While there are no data to inform a specific dose adjustment in renally-impaired patients, the Dosage and Administration section should refer to the appropriate Precaution.

D. Labeling Comments to be Conveyed the Applicant

The following labeling comments will be conveyed to the Applicant. These comments refer to the draft labeling identified as "31July03version," included in the "Proposed Labeling" section of the July 31, 2003 submission.

1. The sentences that previously read "

   have been changed to read "Improvement of lung function was maintained over 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance." [Lines 154-156]. The phrase " is somewhat ambiguous and might be taken to mean that the effect was established beyond 24 hours. Therefore the word " , should be changed to "for."

2. Delete lines 172-177. Replace them with the following sentence:

3. The following statements should be added to the CLINICAL PHARMACOLOGY section of the package insert: "In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline corrected QT interval of 30-60msec was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate."

4. In the CLINICAL PHARMACOLOGY, Mechanism of Action section: the word " (line48) has no particular meaning when used to qualify "antimuscarinic." Delete the word "

5. In the CLINICAL PHARMACOLOGY, Mechanism of Action section: The following two sentences should be deleted: "

16. The OVERDOSAGE section should include reference to a foreign post-marketing report of a case of overdose. This case was referenced in three separate submissions to the Agency (letters dated July 8, 2003, July 22, 2003, and September 29, 2003). This was a female patient of unknown age from Australia, who was prescribed Spiriva for the treatment of COPD. She inhaled 30 capsules over a 2.5 day period and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, Spiriva was discontinued, and the constipation was treated with an enema. Further follow-up was not provided.

17. In the Dosage and Administration insert the following sentence after the sentence ending "...renally-impaired patients." (Line 384): "However, Spiriva use should be monitored closely in patients with moderate to severe renal impairment."

E. Phase 4 Commitments

As discussed in Section II, D, above, ECG data from a randomized, placebo-controlled trial raised the possibility that tiotropium might have a clinically meaningful effect on the QT interval. Although other clinical trials did not raise this potential safety signal, it must be noted that the pivotal trials were not designed and conducted in such a way as to carefully evaluate possible ECG effects. For instance, the protocols for the pivotal trials did not specify the timing of the ECGs in relation to dosing. The Applicant should commit to conduct a clinical study to thoroughly investigate the effects of tiotropium on the QT interval. Such a study could be performed in normal volunteers or COPD patients, should investigate effects following a single dose and at steady state, and should include the proposed marketed dose, as well as a higher dose. The Applicant should submit the proposed study to the Division for comments, prior to initiating the study.

F. Request for Information

As discussed in Section II C, above, the Applicant reports that the Dutch authorities have requested that the Summary of Product Characteristics document be revised to expand the statements regarding allergic reactions. The Applicant has proposed to add reference to post-marketing events of urticaria and pruritis in the US product label. The Applicant should provide further details and explanation regarding the data that generated these concerns.

Comment to Applicant (Information Request)

The application states that the Dutch authorities have requested that the Summary of Product Characteristics document be revised to expand the statements regarding allergic reactions. You have proposed to add reference to post-marketing events of urticaria and pruritis in the US product label. Provide further details and explanation regarding the data that generated these concerns.

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/s/

Eugene Sullivan
12/22/03 03:42:30 PM
MEDICAL OFFICER

Badrul Chowdhury
12/22/03 04:05:40 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21-395	TRADE NAME:	Spiriva
APPLICANT/SPONSOR:		USAN NAME:	tiotropium bromide
MEDICAL OFFICER:	Eugene Sullivan, MD FCCP		
TEAM LEADER:	Badrul Chowdhury, MD PhD	CATEGORY:	Anticholinergic bronchodilator
DUE DATE:	n/a	ROUTE:	Oral inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
November 19, 2002	November 20, 2002	N-000-BL	Labeling amendment

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

This submission represents the Applicant's response to prior labeling comments that were provided by the Division in the form of a draft label, dated October 10, 2002. The Applicant has incorporated most of the changes suggested by the Division, with two significant exceptions. This document will discuss these exceptions as well as a few additional labeling issues, and reach conclusions regarding the product label and Patient's Instructions for Use document.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	SAFE TO PROCEED	___	CLINICAL HOLD	
NDA/SUPPLEMENTS:	___	FILEABLE	___	NOT FILEABLE	
	___	APPROVAL	___	APPROVABLE	___ NOT APPROVABLE
OTHER ACTION:					

The Division has previously communicated recommended labeling changes to the Applicant. These changes were conveyed in the form of a draft label, dated October 10, 2002. This submission includes an updated draft label that incorporates most of the Division's recommended changes. The following issues are still outstanding.

The October 10, 2002 draft label included instruction to the Applicant to amend the two figures representing the data from one of the 6-month studies. [redacted] were to be deleted from the figures. During a November 8, 2002, telecon, the Division agreed to discuss this issue further internally. For that reason, the Applicant has not removed [redacted] from two figures. This issue has subsequently been discussed further within the Agency and a decision has been reached that the lines should be deleted.

The October 10, 2002 draft label included language regarding exclusion criteria in the clinical studies, which was to be added to the first paragraph of the Adverse Reactions section of the label. The Applicant has not added the language, arguing that labels for other long-acting bronchodilators for COPD do not include such language. The Applicant points out that the pivotal studies supporting Salmeterol for this indication included similar cardiovascular exclusion criteria. This is accurate, and the salmeterol label does not describe the exclusion criteria. It should be noted that, according to the medical officer review, the pivotal studies supporting formoterol for COPD did not include similar cardiovascular exclusion criteria. Also of note, while the salmeterol pivotal studies did list narrow-angle glaucoma and symptomatic prostatic hypertrophy or bladder outlet obstruction as exclusion criteria, these criteria were likely included because of the anticholinergic active comparator (ipratropium bromide) included in the study. It should also be noted that the current draft label for tiotropium bromide includes a Precaution regarding patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder outlet obstruction. Considering these issues, it would seem reasonable to require that the label list the exclusions for narrow angle glaucoma, prostatic hypertrophy, and bladder outlet obstruction. The language regarding the cardiovascular exclusions can be deleted.

In the Clinical Studies portion of the Clinical Pharmacology section the Applicant has added language to describe the magnitude of the mean improvement in FEV_1 at 30 minutes after the first dose. This is acceptable. In this section the Applicant has incorporated the Division's previously proposed amendments.

One editorial change should be made in the Overdosage section.

Two further changes should be made in the Patient's Instructions for Use document. The first is to delete the statement that the drug ' [redacted] since this subjective benefit was not firmly established. The second in a minor editorial change.

Comments to Sponsor

1. Make the following changes to the product label:
   - Lines 172-173: Remove the [redacted] Consistent with this change, delete the phrase ' [redacted] from lines 162-163, and the phrase [redacted] from line 171.
   - Line 307: Add the following sentence: "Patients with narrow angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials."
   - Lines 345-347: Replace the sentence beginning with "Bilateral conjunctivitis and..." with the following sentence: " In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141micrograms of tiotropium."
2. Make the following changes to the Patient's Instructions for Use document:
   - Lines 22-23: Replace the first sentence with the following sentence: "SPIRIVA is a once-daily maintenance bronchodilator medicine that opens narrowed airways and helps keep them open for 24 hours."

- Lines 27-28: Replace with the following: "SPIRIVA CAPSULES ARE INTENDED FOR ORAL INHALATION ONLY AND ARE TO BE USED ONLY WITH THE HANDIHALER INHALATION DEVICE."

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/s/

Eugene Sullivan
12/10/02 03:14:09 PM
MEDICAL OFFICER

Badrul Chowdhury
12/10/02 04:24:26 PM
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CLINICAL REVIEW

MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #: 21-395
Sponsor: Boehringer Ingelheim
Investigator: Multiple
Category: Anticholinergic Bronchodilator
Reviewer: Eugene J. Sullivan, MD, FCCP

Application Type: NDA
Proprietary Name: Spiriva
US Adopted Name (USAN)/ International Non-proprietary Name (INN): Tiotropium Bromide
Route of Administration: Oral Inhalation
Review Date: September 20, 2002

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
December 12, 2001	December 14, 2001	Original NDA	
April 12, 2002	April 15, 2002	Response to Request	CMC
April 18, 2002		120-day Safety Update	
July 16, 2002	July 18, 2002	Response to Request	
July 24, 2002	July 25, 2002	Response to Request	Pregnancy data
July 31, 2002	August 1, 2002	Response to Request	Heart rate data

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY: This is the Medical Officer Review of the NDA submitted in support of approval of a new, long-acting, anti-muscarinic bronchodilator, tiotropium bromide dry powder inhaler, for COPD. The Applicant proposed an Indication for treatment of "bronchospasm and dyspnea" associated with COPD. Six pivotal safety and efficacy studies were submitted. These were large, placebo- and/or active-controlled studies of six to twelve months' duration. The studies established the bronchodilator efficacy of the drug, but did not adequately establish a benefit in regard to the symptom of dyspnea. The safety profile of the drug is acceptable. Adverse events seen in the Phase 3 studies primarily reflected a systemic anticholinergic effect.

OUTSTANDING ISSUES: None.

RECOMMENDED REGULATORY ACTION:

NDA, Efficacy/Label supplement: ___X___ **Approvable** _____ **Not Approvable**

Medical Reviewer: Eugene J. Sullivan, MD, FCCP
Division Director: Badrul Chowdhury, MD, Ph.D.

Table of Contents

Clinical Review for NDA 21-395

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, the data submitted in this NDA provide adequate support for Approval. The data demonstrate that regular daily administration of tiotropium bromide inhalation powder (18mcg) provides clinically meaningful bronchodilation in patients with chronic obstructive pulmonary disease (COPD). The primary assessment of the bronchodilator effect was based on a commonly used and accepted clinical endpoint, the forced expiratory volume in one second (FEV_1), and was further supported by appropriate secondary endpoints. The safety profile of tiotropium bromide inhalation powder was acceptable, given its documented clinical efficacy. In the clinical studies, adverse events attributable to the drug were generally non-serious and were likely related to systemic anticholinergic effects. The safety data raised the possibility of a drug effect in regard to cardiac adverse events categorized as "heart rate and rhythm disorders." In addition, the Phase 3 study population differed from the intended population in ways that might impact the safety profile once the drug is marketed. These two issues are discussed in Section I.B., below.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Although the development program provided adequate assurance of safety to allow for marketing approval, certain questions that remain should be investigated during Phase 4. First, the Phase 3 data raised the possibility that the drug may be associated with an increased frequency of adverse events in the category of "heart rate and rhythm disorders." The ECG and Holter monitor data did not identify a drug effect; however, the number of patients who underwent Holter monitoring was relatively small. In the absence of a possible signal in terms of "heart rate and rhythm disorders," the number might have been adequate, but given the concerns raised by the adverse event data it would be reasonable to obtain further Holter data in Phase 4. Second, because of the constitution of the Phase 3 study population, the safety of the drug in patients with concurrent cardiac or renal disease is not known. Such patients are very likely to be exposed to the drug once it is marketed.

Patients with symptomatic benign prostatic hypertrophy or narrow angle glaucoma were also excluded from the Phase 3 studies; however, it may not be appropriate to expose such patients in further clinical trials, given the known anticholinergic effect of the drug. Nonetheless, if approved, it can be expected that such patients may ultimately receive the drug. Therefore, the product label should clearly state that caution should be used in these settings.

C. Recommendations of the Pulmonary-Allergy Drugs Advisory Committee

On September 6, 2002, the Pulmonary-Allergy Drugs Advisory Committee (PADAC) met to discuss this Application. Following presentations from both the Applicant and the Division, and a period of open discussion, the PADAC was asked to address certain questions in regard to the Application. The PADAC unanimously agreed that the data provided substantial and convincing evidence that tiotropium bromide inhalation powder provides a clinically meaningful bronchodilator effect when used in the chronic treatment of patients with COPD. However, they also unanimously agreed that the data did not provide substantial and convincing evidence that the drug provides a clinically meaningful effect for the symptom of dyspnea in patients with COPD. The PADAC voted 8 to 3 in favor of the opinion that the safety database was adequate. Several members indicated that Phase 4 study of patients excluded from the Phase 3 studies should be performed. This included primarily patients with cardiac disease or renal disease. Some members of the PADAC also suggested that additional data should be obtained in racial populations not well represented in the Phase 3 program, which included predominantly Caucasians.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Tiotropium bromide inhalation powder is an anticholinergic bronchodilator intended for oral inhalation. The drug has been developed for use in patients with COPD. A total of 4,124 subjects participated in the clinical program. This included 224 healthy volunteers, 3,411 COPD patients, 471 asthma patients, and 18 patients with renal impairment. A total of 2,117 subjects were exposed to tiotropium by inhalation of the powder capsule formulation. A total of 1,701 subjects were exposed to the proposed marketed dose (18mcg).

The Phase 3 program consisted of six "pivotal" studies in COPD patients, in which a total of 1308 patients were exposed to tiotropium at the proposed marketed dose (18mcg QD). The six Phase 3 studies included three sets of two identical (or nearly identical) studies: 2 one-year, placebo-controlled studies performed in the US (205.114/205.117 and 205.115/205.128); 2 one-year, active (ipratropium bromide)-controlled studies performed in Europe (205.122A/205.126A and 205.122B/205.126B); and 2 six-month, placebo- and active (salmeterol xinafoate)-controlled multinational studies (205.130 and 205.137).

In these studies, eligible patients had a history of COPD, a smoking history ≥ 10 pack-years, age≥ 40 years, and $FEV_1 \leq 65\%$ of predicted and ≤ 70% of FVC. Baseline bronchodilator reversibility was not assessed and was not used to select patients. Patients with a history of asthma, allergic rhinitis, or atopy were excluded, as were patients with a history of siginificant disease other than COPD, symptomatic prostatic hypertrophy or bladder outlet obstruction, narrow angle glaucoma, or active cardiac disease as defined by a history of myocardial infarction within one year, cardiac arrhythmia requiring drug treatment, or hospitalization for heart failure

within 3 years. In the six Phase 3 studies, the patients were 63-65 years of age, with a smoking history of 33-63 pack-years, a duration of COPD of 8-12 years, and a baseline FEV_1 of 1.0 to 1.2 liters. The majority of the patients were men (65-86%), and nearly all were Caucasian (92-100%).

B. Efficacy

The Applicant proposed the following Indication for the drug: "Spiriva is indicated for the long term, once daily, maintenance treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema." The inclusion of the word "dyspnea" in the Indications section of the product label would mark a departure from the language commonly used in the product labels of other medications approved for COPD. The Indications sections of these labels commonly refer to the "treatment of bronchospasm" associated with COPD, reflecting the fact that measures of bronchospasm (e.g. FEV_1) are commonly used to support approval. The Division has generally assumed that improvements in FEV_1 of sufficient magnitude are likely clinically meaningful to patients. Therefore, FEV_1 is an accepted primary efficacy endpoint in Phase 3 studies, in order to support an Indication for treatment of bronchospasm.

Bronchospasm:

In support of its proposal to include reference to both bronchospasm and dyspnea in the Indications section of the product label, the Applicant included measures of bronchospasm and dyspnea among the primary endpoints in the Phase 3 studies. In all six studies, the trough (pre-dose) FEV_1 was included as either a primary or a co-primary endpoint. In two of the six studies (205.130 and 205.137), an index of the symptom of dyspnea, the Mahler Transition Dyspnea Index (TDI), was included a co-primary endpoint.

As stated above, the primary efficacy variable used to establish bronchodilator efficacy was the trough FEV_1 response. This was defined as the change from baseline in the mean of the two FEV_1 values at the end of the dosing interval (approximately 23 and 24 hours post-dosing). Various secondary variables were also used to address bronchodilator efficacy. These included FEV_1 and FVC variables (peak and average) during serial spirometry performed at clinic visits, home, twice-daily peak expiratory flow rates (PEFR), and "rescue" albuterol use.

The one-year, placebo-controlled, US studies enrolled 470 and 450 patients, and utilized a 3:2 (active:placebo) randomization scheme (205.114/205.117 and 205.115/128). The primary efficacy endpoint was the trough FEV_1 response, assessed at 13 weeks. In both studies, tiotropium was statistically superior to placebo on this endpoint ($p=0.0001$), with an effect size of 0.14 liters. Tiotropium was also statistically superior to placebo on this variable at all other clinic visits (Weeks 1, 7, 25, 37, and 49), with mean effect sizes of 0.11 – 0.16 liters. In addition, tiotropium was statistically superior to placebo on the peak FEV_1 and the average FEV_1 during the 3-hour serial spirometry performed at all clinic visits. The mean peak FEV_1 response was 0.24 liters on Day 1 and ranged from 0.25 to 0.31 liters on subsequent clinic visits (Note: these are not placebo-subtracted values). Tiotropium was also statistically superior to placebo in regard to the FVC response (trough, average, and peak) on all visits, and in regard to weekly

mean morning and evening home PEFR for most weeks. Finally, tiotropium was statistically superior to placebo in regard to the "rescue" use of albuterol, with patients on tiotropium using 5-6 fewer doses per week. No consistent, meaningful effect was seen in regard to the occurrence of COPD exacerbations or hospitalizations, or the results of the St. George's Hospital Respiratory Questionnaire or the Medical Outcomes Study SF-36. Based on these findings it can be concluded that tiotropium provides a statistically and clinically significant degree of bronchodilation in this study population.

The one-year, active-controlled, US studies enrolled 288 and 247 patients, and utilized a 2:1 (active:control) randomization scheme (205.122A/205.126A and 205.122B/205.126B). The active control in these studies was ipratropium bromide MDI administered QID. In both studies, tiotropium was statistically superior to ipratropium for the trough FEV_1 response at all clinic visits, with an effect size of 0.11 –0.18 liters. The absence of a placebo control complicates the interpretation of the post-dosing serial spirometry results. Tiotropium was statistically superior to ipratropium in regard to the "rescue" use of albuterol use during 36 of the 52 weeks in one study, but was not superior to ipratropium in the other study. with patients on tiotropium using 5-6 fewer doses per week. No consistent, meaningful effect was seen in regard to the occurrence of COPD exacerbations or hospitalizations. Based on these findings it can be concluded that tiotropium provides a statistically and clinically significant degree of bronchodilation in this study population.

The six-month, placebo- and active-controlled, multinational studies enrolled 623 and 584 patients, and utilized a 1:1:1 randomization scheme (205.130 and 205.137). The active control in these studies was salmeterol xinafoate MDI, administered BID. The trough FEV_1 response assessed at 6 months was one of two co-primary endpoints in these studies. In both studies, tiotropium was statistically superior to placebo on this endpoint (p=0.0001), with mean effect sizes of 0.14 liters and 0.11 liters. Tiotropium was also statistically superior to placebo on this variable at all other clinic visits, with mean effect sizes of 0.11 to 0.15 liters. In addition, tiotropium was statistically superior to placebo for the mean peak FEV_1 and mean average FEV_1 during the 12- or 3-hour serial spirometry performed at all clinic visits. Tiotropium was also statistically superior to placebo in regard to the FVC response (trough, average, and peak) on all visits, and in regard to weekly mean morning and evening home PEFR. Tiotropium was statistically superior to placebo in regard to "rescue" albuterol use in one of the two studies. No consistent, meaningful difference was shown in regard to the occurrence of COPD exacerbations or hospitalizations, or in regard to the results of the St. George's Hospital Respiratory Questionnaire. Based on these findings it can be concluded that tiotropium provides a statistically and clinically significant degree of bronchodilation in this study population.

Dyspnea:

The primary support of the proposed benefit in regard to the symptom of dyspnea was the results of the two 6-month, multinational, placebo- and active-controlled studies, in which the TDI was included as a co-primary endpoint. In a protocol amendment submitted after completion of the studies but prior to unblinding of the data, the Applicant specified a TDI "responder" analysis as a co-primary endpoint, along with the trough FEV_1 response. The "responder" analysis was based on a threshold of +1 for the TDI focal score. The primary endpoint was 6 months. In both

studies, the percentage of responders was statistically greater in the tiotropium group, compared to the placebo group ($p<0.05$) at six months. The percentages of responders in the tiotropium groups was 42% and 45% in the two studies, compared with 26% and 33% in the placebo groups in the two studies. For comparison, the percentages of responders was 35% and 48% in the salmeterol groups in the two studies. Using the combined study data, a number-needed-to-treat analysis revealed that approximately 8 patients would need to be treated to achieve 1 responder (using the proposed threshold of +1 unit) more than would be achieved with placebo. Using the same responder analyses after 8 and 16 weeks of treatment, in both studies, the percentage of responders was statistically greater in the tiotropium, compared to placebo.

In the one-year, placebo-controlled studies, the TDI data was analyzed using mean values. In these studies, the mean TDI focal score was statistically greater in the tiotropium group at all clinic visits (Weeks 7, 13, 25, 37, and 49). However, the difference in mean TDI focal scores between tiotropium and placebo was <1 unit at 7 of the 10 times it was administered.

Interpretation of the significance of the TDI data from these studies is complicated by several factors. First, it is not clear that the TDI instrument has been adequately validated as a reliable measure of dyspnea in long-term clinical drug-intervention studies. Second, it is clear that the instrument was not appropriately implemented in the clinical studies. As above, the decision to elevate the TDI from one of numerous secondary endpoints to a co-primary endpoint was not reached until after the study had been completed. Therefore, the protocols were likely not written with sufficient attention to assure that the instrument was implemented exactly as it was designed to be. Implementation issues include the use of the instrument in several languages for which there is no validated translation, the fact that observers who administered the instrument were not blinded to potentially important clinical data (e.g. the results of the St. George's Hospital Respiratory Questionnaire) and may not have had adequate training, and the fact that at some centers the patients themselves, rather than an observer, may have completed the instrument. Finally, the assertion that a TDI focal score of ≥1 represents a clinically meaningful change has not been adequately demonstrated.

Given the TDI data from the Phase 3 studies and the concerns regarding the TDI instrument and its validation discussed above, it cannot be concluded that tiotropium provides a clinically meaningful benefit in regard to the symptom of dyspnea. This statement is in agreement with the conclusions of the Pulmonary-Allergy Drugs Advisory Committee, as expressed during the September 6, 2002, meeting.

In summary, the efficacy data derived from the Phase 3 program support the approval of tiotropium based on its demonstrated statistically and clinically significant bronchodilator effect,